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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/613,038	07/10/2000	Antonio J. Grillo-Lopez	P1752R1	9334

7590 08/08/2006

Attn Wendy Lee
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EXAMINER
SCHWADRON, RONALD B

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/613,038	GRILLO-LOPEZ ET AL.	
	Examiner	Art Unit	
	Ron Schwadron, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**.. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-10,12-16,22,28 and 32-61* is/are pending in the application.

4a) Of the above claim(s) *61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-10,12-16,22,28 and 32-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/23/06 has been entered.

2. Applicant's election of claims 1,6-10,12-16,22,28,32-60 in the reply filed on 5/8/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claim 61 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/8/06.

4. In view of the papers filed 1/23/06, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by addition of Mark Peskovitz.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The declaration is defective because it includes Timothy Stewart who is no longer an inventor.

6. The rejections of claims 1, 6-16, 22, 28, 32-44, 50-51 and 57-58 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons elaborated in the previous Office Action are withdrawn in view of the amended claims.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 6-16, 22, 28, 32-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

a)There is no support in the specification as originally filed for the recitation of "wherein after a first intravenous administration of said antibody the circulating levels of B cells in the human are reduced to block said immune response" as per recited in claims 1/28. Regarding applicants comments about the specification, pages 8-9, said passage does not disclose that "after a first intravenous administration of said antibody the circulating levels of B cells in the human are reduced to block said immune response". Said passage does not disclose that an immune response is blocked after a first initial dose of antibody. It also does not refer to an immune response per se, it refers to a "humoral response elicited by the B cell" or "one or more B cell functions". There is no written description of the scope of the claimed invention in the specification as originally filed (aka the claimed invention constitutes new matter).

b) There is no support in the specification as originally filed for the recitation of "wherein each administration of the antibody is by intravenous injection" as recited in claims 45/46. Regarding applicants comments about the specification, page 42, whilst said passage discloses intravenous administration,

it does not disclose exclusive use of intravenous administration to the exclusion of other administration routes. In fact, the first sentence of the cited passage indicates that the "antagonist is administered by any suitable means". Said passage also indicates in the last sentence that the use of intravenous or subcutaneous injections will depend in part on whether the administration is brief or chronic. There is no written description of the scope of the claimed invention in the specification as originally filed (aka the claimed invention constitutes new matter).

9. The rejection of claims 45-48,50-55,57-60 under 35 U.S.C. 102(b) as being anticipated by WO 98/04281 (IDS Ref. No. 31) for the reasons set forth in the previous Office Action is withdrawn because the amended claims now require that the antibody is administered only via the intravenous route wherein this is not disclosed in WO 98/04281.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1, 6, 12-16, 22, 28, 34-39, 43,44 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/04281 (IDS Ref. No. 31) for the same reasons set forth in

the previous Office Action mailed 7/28/04. Applicants arguments have been considered and deemed not persuasive.

The `281 publication teaches and claims an improved method of treating immune cell mediated diseases comprising administering to a patient (i.e., human) (page 7, lines 16-21) a therapeutic protein such as a monoclonal antibody (see published claim 1), wherein the immune cell is a B-cell (see published claim 19), wherein the B-cell antigen is human CD20 (see published claim 23), wherein the therapeutic protein is a monoclonal antibody to human CD20 (see published claim 25), wherein the dose is given intravenously (published claim 15) and wherein the B-cell mediated disease is graft verses host disease (see published claim 21 in particular). The `281 publication further teaches that the therapeutic proteins are useful in the treatment of transplanted organ rejection such as heart, lung, kidney, cornea, bone marrow, skin, etc (see page 10 lines 1-3 in particular). In addition, the `281 publication teaches that the monoclonal antibody can be chimeric, human or humanized (see page 7, lines 5-14 in particular). The `281 publication teaches that the administration can be accomplished subcutaneous (see page 7, under Route of Administration) or intravenously (see page 1 line 14-15, page 20, under intravenous administration and tables 1-5). The `281 publication further teaches a dosing regimen encompassed by that recited in the claims (see page 10, lines 28-33 and tables 1-5). The `281 publication teaches that the improvement method comprises administering a dose of therapeutic protein (i.e. anti-CD20), followed by a second administration of said therapeutic protein, wherein the systemic exposure of said therapeutic protein from the second administration is at least 50% greater than the systemic exposure from a first (see published claim 1). The `281 publication teaches prophylactic use in transplanted organ rejection (see page 10, lines 13-14 in particular). While the prior art teachings may be silent as to the "the circulating levels of B cells in the human are reduced to block said immune response" per se; the WO `281 publication exemplifies the reduce circulating levels of B cells using the same antibody. Therefore "the circulating levels of B cells in the human are reduced to block said immune response" is considered inherent properties. Claims 13-15 are included because the specific doses taught by the '281 publication anticipate the claimed rages. Claims 43, 44 are included because the reference dosages are substantially less than 375 mg/m^2. Claim 22 is included because

the `281 publication teaches a prophylactic use in transplanted organ rejection, therefore it will be immediately apparent to administer the antibody to the patient before the patient is exposed to the graft in the prophylactic use of the transplanted organ rejection.

Regarding applicants comments about Bugelski et al., the claimed invention is not drawn to a method of treatment using antiCD4 antibody. Therefore applicants comments are not germane to the invention under consideration. WO 98/04281 and the claimed invention provide equivalent disclosures regarding the use of the claimed method to treat graft rejection (aka both provide zero evidence regarding the actual use of the claimed invention to treat graft rejection). Thus, any post filing date references of record regarding the use of the claimed invention to treat graft rejection are as applicable to WO 98/04281 as the instant invention. The saturating dose of antiCD20 antibody and methods of determining such doses were well known in the art (for example see Reff et al. or US Patent 5,736,137, columns 24-28). The saturating dose disclosed in said references is encompassed by the therapeutic doses recited in the claims. It is also noted that multiple intravenous injections are disclosed by WO 98/04281 (for example see page 10, last paragraph). WO 98/04281 teaches and claims an improved method of treating immune cell mediated diseases comprising administering to a patient a therapeutic protein such as a monoclonal antibody, wherein the immune cell is a B-cell (see published claim 19), wherein the B-cell antigen is human CD20 (see published claim 23), wherein the therapeutic protein is a monoclonal antibody to human CD20 (see published claim 25).

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 6-10, 12-16, 22, 28,32, 34-41, 43,44 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/04281 (IDS Ref. No. 31) in view of Business Wire (2/24/1998) for the same reasons set forth in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

The teachings of WO 98/04281 publication have been discussed, supra. The claimed invention differs from the reference teachings only by the recitation that the antibody comprises rituximab in claims 7,40, 49 and 56, conjugated with a cytotoxic agent in claim 8, Y2B8 in claims 10, 32, and 41 wherein the cytotoxic agent is a radioactive compound in claim 9. The Business Wire article teaches use of IDEC-Y2B8 and RITUXAN (Rituximab), wherein Y2B8 is a monoclonal antibody tightly conjugated to the radioisotope yttrium-90, which targets the CD20 antigen on mature normal and malignant B cells. Further the article teaches that the MX-DTPA used to create IDEC-Y2B8 exhibits excellent in vivo retention of yttrium. Further, studies in mice have shown minimal loss of the radioisotope from the conjugate and not significant accumulation of yttrium in bone. The article further teaches that IDEC Pharmaceuticals focuses on developing targeted therapies for the treatment of cancer and autoimmune diseases, Idec's antibody products act chiefly through immune system mechanisms, exerting their effect by binding to specific, readily targeted immune cells in the patient's blood or lymphatic systems (see the entire article). It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the monoclonal antibody to human CD20 taught by the `281 publication with the Y2B8 and/or RITUXAN antibody as taught by the Business Wire article. One of ordinary skill in the art at the time the

invention was made would have been motivated to do so because IDEC-Y2B8 exhibits excellent in vivo retention of yttrium as taught by Business Wire article. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.
Applicant's arguments are essentially as addressed above.

14. Claims 1, 6-10, 12-16,22,28,33, 34-39,42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/04281 (IDS Ref. No. 31) in view of U.S. Pat. No. 6,498,181 for the same reasons set forth in the previous Office Action mailed 7/28/04.
The teachings of WO 98/04281 publication have been discussed, supra. The claimed invention differs from the reference teachings only by the recitation that the antibody is conjugated with a cytotoxic agent in claim 8, ^{131}I-B1 in claims 10, 33, and 42 wherein the cytotoxic agent is a radioactive compound in claim 9. The `181 patent teaches ^{131}I labeled anti-B1 (Bexxar) mAb, raised to the CD-20 antigens that are expressed on the surface of mature B-cells, is one example of a radiolabelled mAb that has seen successful in treating follicular non-Hodgkins lymphoma in recent clinical trials (see co. 9, lines 19-30 in particular). It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the monoclonal antibody to human CD20 taught by the `281 publication with the $^{131}$I-B1 antibody as taught by the `181 patent. One of ordinary skill in the art at the time the invention was made would have been motivated to do so because ^{131}I-B1 has seen successful in recent clinical trials as taught by `181 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.
Applicant's arguments are essentially as addressed above.

15. Claims 1,6-10,12-16,22,28,32,34-41,43-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer et al. (EP 0332865) in view of Anderson et al. (US Patent 5,736,137).

Meyer et al. teach use of antiB cell antibody to treat transplant rejection (see column 2 and column 3, last two paragraphs). Meyer et al. teach that said antibody can be used unconjugated or conjugated to a toxin or radioisotope (see column 3). Meyer et al. teach that said antibody can be antibodies that bind human B cells (see column 3). Meyer et al. do not teach use of antiCD20 antibody or the particular species of antiCD20 antibodies recited in the claims. Anderson et al. teach that treatment with the chimeric antiCD20 antibody C2B8 (alias Rituximab or RITUXAN) can be used to effectively deplete B cells in vivo (see columns 25-28). C2B8 binds the B cell surface antigen CD20. Anderson et al. teach a dose range encompassed by those recited in the claims (see column 8). Anderson et al. also teach B cell depletion using RITUXAN at a variety of dosages (See TABLE 1), wherein said doses are less than 375 mg/ patient. Meyer et al. teach that the anti B cell antibody used can be chimeric and is cytotoxic to B cells (see page 3). The chimeric antiCD20 antibody C2B8 taught by Anderson et al. has both these properties. Anderson et al. also teach the radiolabelled antibody Y2B8 (see column 30).

Humanized and human antibodies binding a desired target, methods of making said antibodies and the advantage of such antibodies were well known in the art. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Meyer et al. teach that antibody against a B cell surface marker can be administered to treat transplant rejection, while Anderson et al. teach that treatment with the chimeric antiCD20 antibody C2B8 (alias Rituximab) can be used to effectively deplete B cells in vivo at dosages encompassed by those recited in the claims. One of ordinary skill in the art would have been motivated to do the aforementioned because Meyer et al. teach that the anti B cell antibody used can be chimeric and is cytotoxic to B cells, while Anderson et al. teach that C2B8 chimeric antiCD20 antibody effectively depletes B cells when administered in vivo. Anderson et al. teach subcutaneous or intravenous administration of said antibody (see column 7, last paragraph). Anderson et al. teach a dose range

encompassed by those recited in the claims (see column 8). A routineer would have increased the second dose of antibody if the first dose of antibody did not provide the required results. The method also includes use of an immunosuppressive agent (OKT3, see page 3, last paragraph).

16. Claims 10,33,42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer et al. (EP 0332865) in view of Anderson et al. (US Patent 5,736,137) as applied to claims 1,6-10,12-16,22,28,32,34-41,43-60 above, and further in view of U.S. Pat. No. 6,498,181.

The previous rejection renders obvious the claimed invention except for use of ^{131}I-B1. The `181 patent teaches ^{131}I labeled anti-B1 (Bexxar) mAb, raised to the CD-20 antigens that are expressed on the surface of mature B-cells, is one example of a radiolabelled mAb that has seen successful in treating follicular non-Hodgkins lymphoma in recent clinical trials (see co. 9, lines 19-30 in particular). It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the monoclonal antibody to human CD20 taught by the `281 publication with the $^{131}$I-B1 antibody as taught by the `181 patent. One of ordinary skill in the art at the time the invention was made would have been motivated to do so because ^{131}I-B1 has seen successful in vivo in humans. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claims 1,6,7,13,22,45,47,49,50 are rejected under 35 U.S.C. 102(a) as being anticipated by Perrotta et al.

The claims under consideration encompass a method of blocking an immune response in a human that has not received a graft. Perrotta et al. disclose treat with rituximab (aka the chimeric antiCD20 antibody formerly known as C2B8) via multiple infusions (aka intravenous infusion) at a dosage encompassed by that recited in the claims wherein the antibody would inherently have the properties recited in the claim because it is the

same antibody as recited in the claims administered at the same concentration. The patient did not suffer from a malignancy. Rituximab is unconjugated C2B8.

18. Claims 1,6-10,13-15,22,32-36,43,45,47-53 rejected under 35 U.S.C. 102(e) as being anticipated by Goldenberg et al. (US 2003/0133930).
The claims under consideration encompass a method of blocking an immune response in a human that has not received a graft. Goldenberg et al. disclose intravenous treatment of patients with antiCD20 antibody including C2B8 or I131 labeled B1 at dosages encompassed by those recited in the claims wherein the antibody would inherently have the properties recited in the claims because it is the same antibody as recited in the claims (see [0089], claims 1,2,12, [0004]), administered at the same concentration. The patient did not suffer from a malignancy. The antibody can be conjugated with a radiolabel or toxin (see claim 31). The antibody can be humanized or human (see [0025] and [0028]).

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron, Ph.D. whose telephone number is 571 272-0851. The examiner can normally be reached on Monday-Thursday 7:30-6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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